937,724

PATENT SPECIFICATION

NO DRAWINGS

937,724

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International Classification:—C07d.

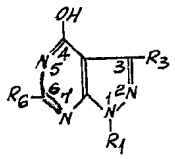
COMPLETE SPECIFICATION

New Pyrazolo-Pyrimidines and process for the preparation thereof

We, CIBA LIMITED, a body corporate organised according to the laws of Switzerland, of Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to new pyrazolo-pyrimidines, a process for their preparation and pharmaceutical preparations containing them.

The present invention provides a pyrazolo-[3,4-d]pyrimidine of the formula



or its tautomeric forms, and salts of these compounds. In the above formula R_1 represents a hydrogen atom, an alkyl, hydroxy-alkyl or oxa-alkyl group, a cycloalkyl, cycloalkyl-alkyl or aralkyl group or an at most binuclear aryl or heterocyclic group. Examples of such substituents are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl-(1), pentyl-(2), pentyl-(3), 2-methyl-butyl-(3) or hexyl groups, 3 - oxa - pentyl- or 5 - oxa - heptyl - (2) groups, hydroxy - lower alkyl - groups, such as hydroxy - ethyl groups, cyclopentyl or cyclohexyl groups, cyclopentyl- or cyclohexyl-methyl, -ethyl or -propyl groups, phenyl-alkyl, such as 1- or 2-phenyl-ethyl or phenylmethyl, or phenyl groups in which the aromatic nuclei may bear substituents, for example lower alkyl or free or substituted hydroxyl or amino groups, halogen atoms, trifluoromethyl or nitro groups, or if desired correspondingly substituted mononuclear heterocyclic groups, such as pyridyl, thienyl or furyl groups. In the aforementioned substituted hydroxyl or amino groups, the substituents are preferably those of the aforementioned kind, above all lower alkyl groups, these groups therefore being for example methoxy, ethoxy, propoxy, butoxy, alkylenedioxy groups, such as methylenedioxy groups, mono- or di-alkylamino groups, such as mono- or di-methyl, -ethyl-, -propyl-, -butyl- or -pentylamino groups. As halogen atoms there may be mentioned more especially fluorine, chlorine or bromine.

R_3 stands for a hydrogen atom, or secondly for a lower alkyl group, for example one of those mentioned above for R_1, particularly methyl.

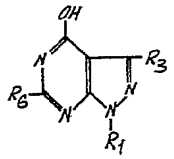
R_6 represents an aralkyl group in which the alkyl groups are, for example, methyl, ethyl, propyl or butyl groups. R_6 is, for example, a phenylalkyl group, such as a 1- or 2-phenyl-ethyl, 1-phenylpropyl or phenylmethyl group in which the aromatic nuclei may bear substituents, such as lower alkyl or free or substituted hydroxyl or amino groups, halogen atoms, trifluoromethyl or nitro groups. The alkyl groups of the aralkyl groups may also be substituted, for example by one of the aforementioned aryl groups, such, for example, as in the diphenylmethyl group. Substituted hydroxyl or amino groups on the phenyl nuclei are, for example, those mentioned above for R_1, more especially lower alkoxy groups, such as methoxy, ethoxy, propoxy, butoxy or methylenedioxy or dimethylamino groups; a preferred halogen atom is a chlorine atom.

The term "lower" in qualifying the hydrocarbon groups is used herein to mean those groups containing up to 7 carbon atoms.

The new compounds have valuable pharmacological properties. More especially they have

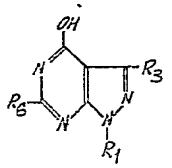
a coronary dilatating action. The new compounds may be used as medicaments, particularly in circulatory disturbances of the myocardium, but also as intermediate products for the preparation of such medicaments.

Especially valuable as coronary dilatating agents are compounds of the formula



and its tautomeric forms and the salts thereof, in which R_1 represents a hydrogen atom or a lower alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl-(2), 3-methyl-butyl-(2), pentyl-(2), pentyl-(3), cycloalkyl, for example cyclopentyl or cyclohexyl, hydroxy-lower alkyl, such as hydroxy ethyl, oxa-lower alkyl, such as 3-oxapentyl, or an aryl such as a phenyl group; the aryl group may be unsubstituted or mono-, di- or tri-substituted by halogen, such as chlorine or bromine, alkoxy, such as methoxy or ethoxy, alkyl, such as methyl, ethyl, propyl, isopropyl, butyl or tertiary butyl, methylenedioxy, trifluoromethyl, nitro or amino groups, or it may represent a pyridyl group, R_3 represents a hydrogen atom or lower alkyl and R_6 an aralkyl, such as a phenylalkyl, and above all a phenylmethyl group; the aryl groups may be substituted as defined above.

Especially valuable are, furthermore, compounds of the formula



as well as their tautomers and salts thereof, in which R_1 stands for a lower alkyl group, R_3 for a lower alkyl group or especially hydrogen and R_6 for an unsubstituted benzyl group or a benzyl group mono-, di- or tri-substituted in the phenyl nucleus by chlorine, methoxy, methylenedioxy, methyl or trifluoromethyl.

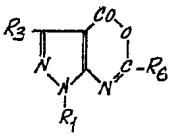
There may be mentioned more especially: 1 - isopropyl - 4 - hydroxy - 6 - *p* - chlorobenzyl - pyrazolo[3,4-d]pyrimidine, 1 - isopropyl - 4 - hydroxy - 6 - *m* - methoxybenzyl - pyrazolo[3,4-d]pyrimidine, 1 - isopropyl - 4 - hydroxy - 6 - (3^1:4^1:5^1 - trimethoxyphenyl - methyl) - pyrazolo[3,4-d]-pyrimidine and 1 - pentyl - (3^1) - 4- hydroxy-6 - benzyl - pyrazolo[3,4-d]pyrimidine and their salts.

The new compounds are obtained in a manner known *per se*, for example by reacting a 2 - R_1 - 3 - amino - 5 - R_3 - pyrazole - 4-carboxylic acid ester with a carboxylic acid of the formula R_6-COOH in the form of its amide or nitrile, or reacting a 2 - R_1 - 3-amino - 5 - R_3 - pyrazole - 4 - carboxylic acid amide with the carboxylic acid of the formula R_6-COOH in the form of its anhydride, or amide, or with a corresponding halide or nitrile.

The reaction may also be performed by first acylating the amino group of the 3 - amino - 2-R_1 - pyrazole - 5 - R_3 - 4 - carboxylic acid amide with the carboxylic acid of the formula R_6COOH in the form of its anhydride or halide, and in the second reaction step the ring is closed.

The condensation of the aminopyrazoles or, if desired, of the acylated aminopyrazoles to the pyrazolo-pyrimidines, is preferably carried out at a raised temperature, if desired in the presence of a diluent and/or condensing agent, under atmospheric or superatmospheric pressure. In this connection it has been surprisingly found that it is very advantageous to perform the reaction with the use of a 2 - R_1 - 3-amino - 5 - R_3 - pyrazole - 4 - carboxylic acid ester, for example the alkyl ester, and of a nitrile of the formula R_6-CN using a condensing agent, preferably an alkali metal, for example sodium, if desired in the form of its amide, hydride or of an alcoholate, or another strong base, such as trimethylbenzyl-ammonium hydroxide and a diluent such as benzene, toluene, xylene or an ether.

The invention also includes any modification of the process in which an intermediate product obtained at any stage of the process is used as starting material and the remaining process steps are carried out, or in which the starting materials or intermediates are formed in the course of the reaction. Of special importance is that modification of the process in which the 2 - R_1 - 3 - amino - 5 - R_3 - pyrazole - 4-carboxylic acid amide is replaced by a derivative convertible thereinto, for example the nitrile, and the latter is converted into the amide after the reaction with the derivative of the acid R_6COOH for example by treatment with an alkali in the presence of an oxidizing agent, such as hydrogen peroxide, with or without isolation of the intermediate product formed in this reaction, and the ring is then closed to form the 4-hydroxypyrazolo[3,4-d]-pyrimidine. Another process in which an intermediate product is formed under the reaction condition is, for example, the reaction of a compound of the formula



with ammonia, the acid amide being formed intermediarily. These oxazines are obtained, for example, by eliminating water from 2 - R_1 - 3 - (R_6 - CONH) - 4 - carboxy-pyrazoles, for example by means of an anhydride, such as acetic anhydride. In the resulting compounds substituents may be converted into one another within the groups mentioned. For example a nitrophenyl group may be reduced in conventional manner to an aminophenyl group or a phenyl radical nitrated.

The above reactions are performed in the ordinary manner, if desired in the presence of a diluent and/or condensing agent and/or catalyst, at ordinary temperatures or, if desired, a raised temperature.

The resulting hydroxy compounds may be converted in the ordinary manner into their salts with bases, for example metal salts, such as alkali metal salts, for example sodium or potassium salts, for example by treatment with a corresponding base, for example an alkali metal hydroxide. The salts may be converted into the free hydroxy compounds, advantageously by treatment with acids.

The new, pharmacologically valuable compounds and their salts may be used, for example, in the form of pharmaceutical preparations. The latter contain the above compounds in admixture or conjunction with an organic or inorganic pharmaceutical excipient suitable for enteral or parenteral administration. Suitable excipients are substances which do not react with the new compounds, for example gelatine, lactose, starches, magnesium stearate, talc, vegetable oils, water, benzyl alcohols, gums, polyalkyleneglycols, cholesterol or any other known excipient. The pharmaceutical preparations may be, for example, tablets or dragees or in liquid form as solutions, suspensions or emulsions. They may be sterilized and/or contain assistants, such as preservatives, stabilizers, wetting or emulsifying agents. They may also contain other therapeutically valuable substances. The preparations are formulated by the usual methods. They contain, for example, 5 to 50 mg, preferably 10 mg, of the active substance per dosage unit, and about 1 to 70%, preferably 5 to 50%, of active substance.

The final products of the present process are also valuable intermediate products, for example for the manufacture of the corresponding 4-amino compounds described in our British Application 17106/61 (Serial No. 937,725) or the corresponding 4-mercapto compounds described in our British Application No. 17107/61 (Serial No. 937,726).

It is possible, for example, to replace a hydroxyl group in position 4 of 1-R_1-3-R_3-6-R_6-pyrazolo[3,4-d]pyrimidines by a halogen atom, such as chlorine or bromine, for example by treatment with a halide of phosphoric acid, such as phosphorus oxychloride or phosphorus pentachloride, or to convert it into a free mercapto group in the customary manner, for example by treatment with phosphorus pentasulphide. In a resulting 4-halogeno compound the halogen can be exchanged in the customary manner, for example by reaction with thiourea, a metal salt of hydrogen sulphide or a mercaptan, or with ammonia, an amine or hydrazine. Free mercapto groups may be substituted as shown above and free or substituted mercapto groups replaced by corresponding groups by reaction with ammonia, an amine or a hydrazine.

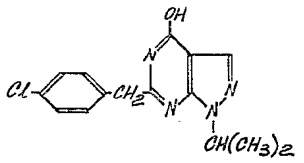
Any new starting material used in the present process may be prepared by a conventional method known *per se*.

Preferred starting materials for use in the present invention are those which yield the final products described above as being particularly valuable. If desired, the starting materials may be used in the form of their salts.

The following Examples illustrate the invention:

EXAMPLE 1

2.3 grams of finely distributed sodium are introduced into a melt of 50 grams of para-chlorobenzyl cyanide and 9.9 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole. The mixture is then heated for 4 hours at 110—120°C with stirring, allowed to cool, mixed with 100 cc of alcohol and evaporated to dryness under vacuum. The residue is taken up in 150 cc of 2N-sodium hydroxide solution, the alkaline solution is freed from the undissolved material by extraction with chloroform and then adjusted with 6N-hydrochloric acid to a pH value of 5—6, whereupon a solid product precipitates which is recrystallized from alcohol, to yield 1 - isopropyl - 4-hydroxy - 6 - para - chlorobenzyl - pyrazolo-[3:4-d]pyrimidine of the formula



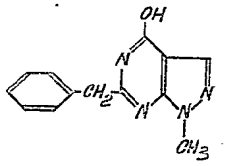
in colourless crystals melting at 181—182°C.

EXAMPLE 2

16.8 grams of 2-isopropyl-3-amino-4-carbon-amido-pyrazole are refluxed for 10 hours in 60 cc of *p*-chloro-benzyl cyanide, allowed to cool and then considerably concentrated under vacuum. The residue is treated with 2N-sodium hydroxide solution and extracted twice with chloroform. The alkaline aqueous solution is treated with carbon and filtered. The filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon the 1-isopropyl-4 - hydroxy - 6 - *p* - chloro - benzyl - pyrazolo-[3,4-d]pyrimidine described in Example 1 precipitates.

EXAMPLE 3

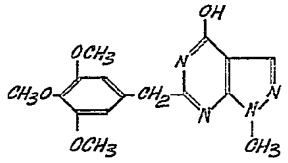
A solution of 8.5 grams of 2-methyl-3-amino-4-carbethoxy-pyrazole in 50 cc of benzyl cyanide is treated with 2.3 grams of sodium in small pieces and the whole is then heated with stirring to 110—120°C. After 4 hours the reaction mixture is cooled and treated with 100 cc of ethanol. The solution is evaporated to dryness under vacuum. The residue is treated with 150 cc of 2N-sodium hydroxide solution and the excess benzyl cyanide is extracted with chloroform. The aqueous phase is adjusted with 5N-hydrochloric acid to a pH value of 5—6, whereupon a solid precipitate forms which is filtered off and repeatedly recrystallized from ethanol, to yield 1 - methyl - 4 - hydroxy - 6 - benzyl-pyrazolo[3,4-d]pyrimidine of the formula



in crystals melting at 236—237°C.

EXAMPLE 4

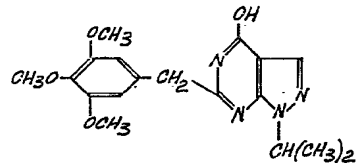
A mixture of 8.5 grams of 2-methyl-3-amino-4-carbethoxy-pyrazole and 50 grams of 3,4,5-trimethoxy-benzyl cyanide is heated to 110°C and 2.3 grams of sodium in small pieces are stirred. After 4 hours the reaction mixture is cooled, treated with 150 cc of ethanol and then evaporated under vacuum. The residue is treated with 150 cc of 2N-sodium hydroxide solution and extracted with chloroform. The aqueous phase is separated and adjusted with 5N-hydrochloric acid to a pH value of 5—6. The resulting precipitate is recrystallized from chloroform+petroleum ether, to yield 1 - methyl - 4 - hydroxy - 6-(3^1,4^1,5^1 - trimethoxy - phenyl - methyl)-pyrazolo[3,4-d]pyrimidine of the formula



in crystals melting at 245°C.

EXAMPLE 5

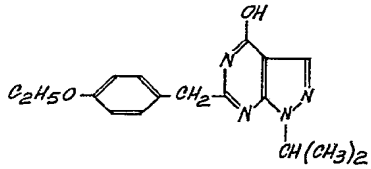
A mixture of 50 grams of 3,4,5-trimethoxy-benzyl cyanide and 9.9 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole is heated to 80°C and 2.3 grams of sodium in small pieces are then added. The mixture is heated for 4 hours at 110—120°C, allowed to cool, the excess sodium is destroyed with alcohol and the whole is evaporated to dryness under vacuum. The residue is taken up in 200 cc of 2N-sodium hydroxide solution and extracted with 200 cc of chloroform to remove excess trimethoxy-benzyl cyanide. The aqueous alkaline solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1 - isopropyl - 4 - hydroxy - 6-(3^1,4^1,5^1 - trimethoxy - phenyl - methyl)-pyrazolo[3,4-d]pyrimidine of the formula



settles out; after recrystallization from alcohol it melts at 195—196°C.

EXAMPLE 6

A mixture of 30 grams of para-ethoxy-benzyl cyanide and 9.9 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole is heated to 60° and 2.3 grams of sodium in small pieces are then added. The mixture is heated for 4 hours at 110—120°C, allowed to cool, the excess sodium is destroyed with alcohol and the whole is evaporated to dryness under vacuum. The residue is taken up in 200 cc of 2N-sodium hydroxide solution and extracted with 200 cc of chloroform to remove excess ethoxy-benzyl cyanide. The aqueous alkaline solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1 - isopropyl - 4 - hydroxy - 6-para - ethoxybenzyl - pyrazolo[3,4-d]-pyrimidine of the formula

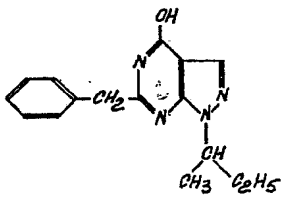


settles out; after recrystallization from alcohol it melts at 175—176°C.

EXAMPLE 7

13.8 grams of sodium in small pieces are added to 200 cc of benzyl-cyanide and 63.3 grams of 2-secondary butyl-3-amino-4-carbethoxy-pyrazole are then added. The mixture is heated during the course of about 30 minutes to 110—120°C and stirred at the same temperature for another 5 hours, allowed to cool, treated with absolute alcohol and evaporated under vacuum. The residue is treated with dilute sodium hydroxide solution and

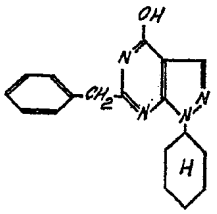
extracted with chloroform. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1-secondary butyl-4-hydroxy-6-benzyl-pyrazolo[3,4-d]pyrimidine of the formula



settles out; after recrystallization from alcohol it melts at 154—155°C.

EXAMPLE 8

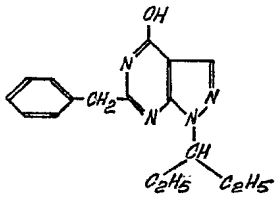
9.2 grams of sodium in small pieces and then 47.4 grams of 2-cyclohexyl-3-amino-4-carbethoxy-pyrazole are added to 130 cc of benzyl cyanide. The mixture is heated within about 30 minutes to 110—120°C and stirred on at the same temperature for 5 hours, allowed to cool, treated with absolute alcohol and evaporated under vacuum. The residue is mixed with dilute sodium hydroxide solution and extracted with chloroform. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1 - cyclohexyl - 4 - hydroxy - 6-benzyl - pyrazolo[3,4-d]pyrimidine of the formula



settles out; after recrystallization from alcohol it melts at 207—208°C.

EXAMPLE 9

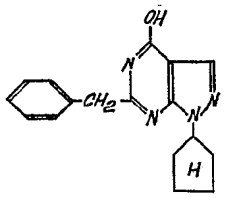
4.6 grams of sodium and then 17 grams of 2 - (3^1 - pentyl) - 3 - amino - 4 - carbethoxy-pyrazole are added to 66 cc of benzyl cyanide. The mixture is heated during the course of about 30 minutes to 110—120°C and then stirred for a further 5 hours at the same temperature, allowed to cool, treated with absolute alcohol and evaporated under vacuum. The residue is treated with dilute sodium hydroxide solution and extracted with chloroform. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1 - (3^1 - pentyl) - 4 - hydroxy - 6 - benzyl - pyrazolo-[3,4-d]pyrimidine of the formula



settles out; after recrystallization from absolute alcohol it melts at 144—145°C.

EXAMPLE 10

3.22 grams of sodium and then 15.61 grams of 2 - cyclopentyl - 3 - amino - 4 - carbethoxy-pyrazole are added to 46 cc of benzyl cyanide. The mixture is heated during the course of about 30 minutes to 110—120°C and stirred for a further 5 hours at the same temperature, allowed to cool, treated with absolute alcohol and evaporated under vacuum. The residue is treated with dilute sodium hydroxide solution and extracted with chloroform. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1 - cyclopentyl - 4 - hydroxy - 6-benzyl - pyrazolo[3,4-d]pyrimidine of the formula

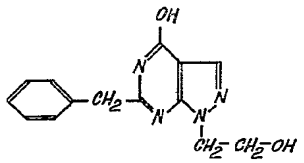


settles out; after recrystallization from absolute alcohol it melts at 189—190°C.

EXAMPLE 11

20.7 grams of sodium in small pieces and then 59.7 grams of 2-(β-hydroxyethyl)-3-amino-4-carbethoxy-pyrazole are added to 250 cc of benzyl cyanide. The mixture is heated during the course of about 30 minutes to 110—120°C and stirred for a further 5 hours at the same temperature, allowed to cool, treated with absolute alcohol and evaporated under vacuum. The residue is treated with dilute sodium hydroxide solution and extracted with chloroform. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 4, whereupon 1 - (β - hydroxyethyl) - 4 - hydroxy - 6-

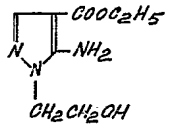
benzyl - pyrazolo[3,4 - d]pyrimidine of the formula



settles out; after recrystallization from alcohol it melts at 194—195°C.

2 - (β - hydroxyethyl) - 3 - amino - 4-carbethoxy - pyrazole used as starting material is prepared in the following manner:

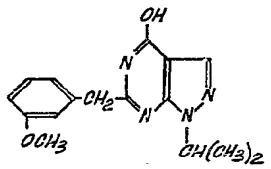
101.5 grams of ethoxymethylene cyanoacetic ester and 66 grams of β-hydroxyethyl hydrazine of 70% strength are heated in 700 cc of alcohol for 10 hours at the boil. The mixture is then evaporated under vacuum and the residue is distilled under vacuum. 2 - (β-hydroxyethyl) - 3 - amino - 4 - carbethoxy-pyrazole of the formula



boils at 180°C under a pressure of 0.6 mm Hg and melts at 89—91°C.

EXAMPLE 12

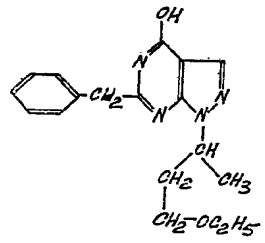
2.3 grams of finely distributed sodium are added to a solution of 9.9 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole in 100 cc of meta-methoxy-benzyl cyanide. The whole is heated with stirring during the course of 4 hours to 110—120°C, allowed to cool, treated with 100 cc of alcohol and evaporated to dryness under vacuum. The residue is taken up in 150 cc of 2N-sodium hydroxide solution, the alkaline solution is extracted with chloroform to remove the insoluble material and then adjusted with 6N-hydrochloric acid to a pH value of 6, whereupon a smeary product settles out which is recrystallized from a small amount of alcohol, to yield 1 - isopropyl - 4 - hydroxy-6 - (meta - methoxy - benzyl) - pyrazolo-[3,4-d]pyrimidine of the formula



in colourless crystals melting at 155—158°C.

EXAMPLE 13

2.3 grams of sodium in small pieces are added to 15 grams of 2 - [1¹ - ethoxy - butyl-(3¹)] - 3 - amino - 4 - carbethoxy - pyrazole and 50 grams of benzyl cyanide and the whole is heated with stirring during the course of 4 hours to 100—110°C, allowed to cool, treated with 150 cc of ethanol and evaporated to dryness under vacuum; the residue is treated with 150 cc of 2N-sodium hydroxide solution and extracted with chloroform. The aqueous solution is acidified with hydrochloric acid and extracted with chloroform, dried and evaporated and the residue is crystallized from aqueous methanol, to yield 1 - [1¹ - ethoxy-butyl - (3¹)] - 4 - hydroxy - 6 - benzyl-pyrazolo[3,4-d]pyrimidine of the formula



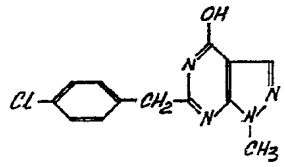
in crystals melting at 111—112°C.

2 - [1¹ - ethoxy - butyl - (3¹)] - 3 - amino-4 - carbethoxy - pyrazole used as starting material is prepared in the following manner:

A mixture of 50 grams of 1-ethoxy-butyl-(3)-hydrazine and 70 grams of ethoxymethylene cyanoacetic ester is boiled for 3 hours in 40 cc of alcohol, evaporated under vacuum and the residue is distilled in a high vacuum. The aforementioned compound boils at 120—125°C under 0.1 mm Hg pressure.

EXAMPLE 14

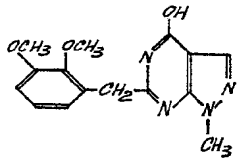
2.3 grams of sodium are added to a mixture of 8.5 grams of 2-methyl-3-amino-4-carbethoxy-pyrazole and 50 grams of para-chlorobenzyl cyanide, the whole is heated for 4 hours at 110°C, allowed to cool, treated with 150 cc of ethanol and evaporated under vacuum. The residue is treated with 150 cc of 2N-sodium hydroxide solution and extracted with chloroform. The aqueous solution is filtered and adjusted with 2N-hydrochloric acid to a pH value of 5—6, whereupon 1 - methyl - 4-hydroxy - 6 - para - chlorobenzyl - pyrazolo-[3,4-d]pyrimidine of the formula



settles out; after recrystallization from aqueous dimethyl formamide it melts at 268—270°C.

EXAMPLE 15

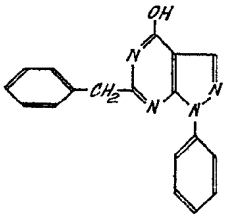
2.3 grams of sodium in small pieces are added to a mixture of 8.5 grams of 2-methyl-3-amino-4-carbethoxy-pyrazole and 50 grams of 2:3-dimethoxy-benzyl cyanide. The mixture is heated for 4 hours at 110°C, allowed to cool, treated with 100 cc of methanol and evaporated to dryness. The residue is treated with 100 cc of 2N-sodium hydroxide solution and extracted with chloroform. On addition of 2N-hydrochloric acid to the alkaline aqueous solution, 1 - methyl - 4 - hydroxy - 6 - (2^1,3^1-dimethoxy - phenyl - methyl) - pyrazolo-[3,4 - d]pyrimidine of the formula



settles out; after recrystallization from alcohol it melts at 190—191°C.

EXAMPLE 16

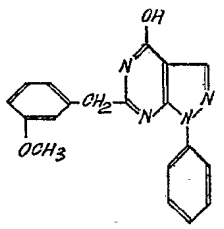
2.3 grams of sodium in small pieces are added to a mixture of 12 grams of 2-phenyl-3-amino-4-carbethoxy-pyrazole and 50 grams of benzyl cyanide and the whole is heated with stirring for 4 hours at 140°C, allowed to cool, treated with 100 cc of alcohol and adjusted with 2N-hydrochloric acid to a pH value of 5—6. The resulting precipitate is recrystallized from chloroform + petroleum ether to yield 1-phenyl-4-hydroxy-6-benzyl-pyrazolo-[3,4-d]pyrimidine of the formula



in colourless crystals melting at 264—265°C.

EXAMPLE 17

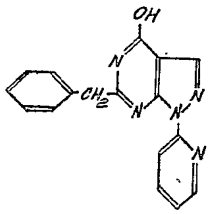
2.3 grams of sodium in small pieces are added to a mixture of 12 grams of 2-phenyl-3-amino-4-carbethoxy-pyrazole and 50 grams of meta-methoxy-benzyl cyanide and the whole is heating with stirring for 4 hours at 110°C, allowed to cool, treated with 100 cc of alcohol and adjusted with 2N-hydrochloric acid to a pH value of 5—6. The resulting precipitate is recrystallized from chloroform + petroleum ether to yield 1-phenyl-4-hydroxy-6-(meta-methoxybenzyl)-pyrazolo[3,4-d]pyrimidine of the formula



in colourless crystals melting at 235°C.

EXAMPLE 18

2.3 grams of sodium in small pieces are added to a mixture of 12 grams of 2α-pyridyl-3-amino-4-carbethoxy-pyrazole and 50 grams of benzyl cyanide. The mixture is then heated for 4 hours at 110°C, allowed to cool, treated with 50 cc of ethanol and evaporated to dryness. The residue is treated with 100 cc of 2N-sodium hydroxide solution and extracted with chloroform. On addition of 2N-hydrochloric acid to the alkaline aqueous solution, 1 - α - pyridyl - 4 - hydroxy - 6 - benzyl-pyrazolo[3,4 - d]pyrimidine of the formula



settles out which is purified by recrystallization from dimethyl formamide. It melts above 360°C.

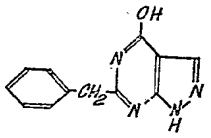
2 - α - pyridyl - 3 - amino - 4 - carbethoxy-pyrazole used as starting material is prepared in the following manner:

A mixture of 35 grams of 2-hydrazino-pyridine, 55 grams of ethoxymethylene-cyano-acetic ester and 200 cc of ethanol is refluxed for 6 hours. The solvent is distilled off under vacuum. The solid residue obtained is recrystallized from alcohol, to yield the aforesaid compound in crystals melting at 95—96°C.

EXAMPLE 19

4.6 grams of finely distributed sodium and 15.5 grams of 3-amino-4-carbethoxy-pyrazole are added to 100 cc of benzyl cyanide. The mixture is heated with stirring for 4 hours at 110—120°C, allowed to cool, treated with 150 cc of ethanol and evaporated to dryness under vacuum. The residue is taken up in 150 cc of 2N-sodium hydroxide solution, the

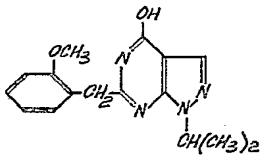
alkaline solution is agitated with chloroform to remove any undissolved material and then adjusted with 6N-hydrochloric acid to a pH value of 4—5, whereupon a solid product precipitates which is recrystallized from much ethanol, to yield 4-hydroxy-6-benzyl-pyrazolo-[3,4-d]pyrimidine of the formula



in colourless crystals melting at 290—292°C.

EXAMPLE 20

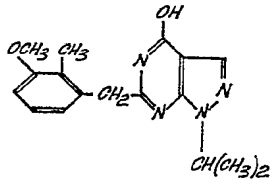
A mixture of 40 grams of ortho-methoxybenzyl cyanide and 9.9 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole is heated to 60°C and 2.3 grams of sodium in small pieces are then added. The mixture is heated for 4 hours at 110—120°C, allowed to cool, the excess sodium is destroyed with ethanol and the whole is evaporated to dryness under vacuum. The residue is taken up in 200 cc of 2N-sodium hydroxide solution and extracted with 200 cc of chloroform to remove the excess ortho-methoxybenzyl cyanide. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1 - isopropyl - 4-hydroxy - 6 - (ortho - methoxybenzyl) - pyrazolo[3,4 - d]pyrimidine of the formula



settles out; after recrystallization from ethanol it melts at 157—159°C.

EXAMPLE 21

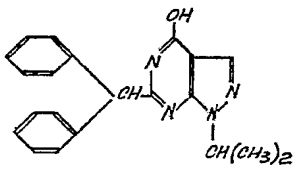
A mixture of 50 grams of 2-methyl-3-methoxybenzyl cyanide and 9.9 grams of 2 - isopropyl - 3 - amino - 4 - carbethoxy-pyrazole is heated to 60°C and 2.3 grams of sodium in small pieces are then added. The mixture is heated for 4 hours at 110—120°C, allowed to cool, the excess sodium is destroyed with ethanol and the reaction mixture is evaporated to dryness under vacuum. The residue is taken up in 200 cc of 2N-sodium hydroxide solution and extracted with 200 cc of chloroform to remove the excess 2-methyl-3-methoxybenzyl cyanide. The alkaline aqueous solution is treated with active carbon and filtered. The clear filtrate is adjusted with 5N-hydrochloric acid to a pH value of 6, whereupon 1 - isopropyl - 4 - hydroxy - 6-(2^1 - methyl - 3^1 - methoxy - phenyl - methyl)-pyrazolo[3,4 - d]pyrimidine of the formula



settles out; after recrystallization from ethanol it melts at 150—151°C.

EXAMPLE 22

A mixture of 20 grams of diphenyl acetonitrile and 19.7 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole is heated to 70°C and 2.3 grams of sodium in small pieces are then added. The mixture is heated for 4 hours at 110—120°C, allowed to cool, the excess sodium is destroyed with ethanol and the mixture is evaporated to dryness under vacuum. The residue is treated with 300 cc of water and the whole is adjusted with 2N-hydrochloric acid to a pH value of 3, whereupon a solid precipitate settles out which is suctioned off, boiled with a large quantity of petroleum ether to remove the residual starting material and the material that did not dissolve in petroleum ether is recrystallized from ethanol, to yield 1 - isopropyl - 4-hydroxy - 6 - diphenylmethyl - pyrazolo-[3,4 - d]pyrimidine of the formula

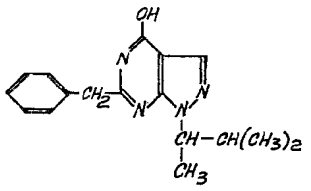


in white crystals melting at 226—227°C.

EXAMPLE 23

2.3 grams of finely distributed sodium and 11.45 grams of 2 - [3^1 - methyl - butyl-(2^1)] - 3 - amino - 4 - carbethoxy - pyrazole are added to 50 cc of benzyl cyanide. The mixture is heated with stirring for 4 hours at 110—120°C, allowed to cool, treated with 100 cc of ethanol and evaporated to dryness under vacuum. The residue is taken up in 150 cc of 2N-sodium hydroxide solution, the alkaline solution is agitated with chloroform to remove the undissolved material and then adjusted with 6N-hydrochloric acid to a pH value of 3; a solid product precipitates which is recrystallized from a little ethanol, to yield 1 - [3^1 - methyl - butyl - (2^1)] - 4 - hydroxy-

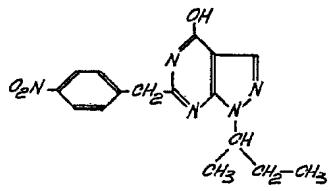
6 - benzyl - pyrazolo[3,4 - d] - pyrimidine of the formula



in colourless crystals melting at 157—158°C.

EXAMPLE 24

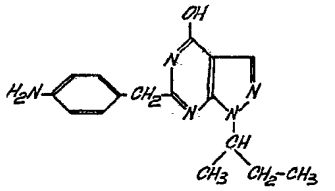
A solution of 13 grams of 1-secondary butyl - 4 - hydroxy - 6 - benzyl - pyrazolo-[3,4 - d]pyrimidine in 100 cc of concentrated sulphuric acid is slowly treated stirring at 0—5°C with 50 cc of concentrated nitric acid. The mixture is kept for 3 hours at room temperature, the reaction solution is poured over ice, the precipitate is suctioned off and repeatedly recrystallized from ethanol, to yield 1-secondary butyl - 4 - hydroxy - 6 - (para-nitrobenzyl) - pyrazolo[3,4 - d]pyrimidine of the formula



in yellowish crystals melting at 181—184°C.

EXAMPLE 25

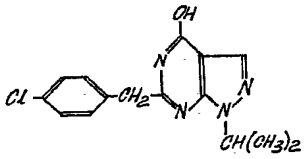
A solution of 15.6 grams of 1 secondary butyl - 4 - hydroxy - 6 - para - nitrobenzyl-pyrazolo[3,4 - d]pyrimidine in 500 cc of ethanol is hydrogenated at room temperature with 4 grams of nickel catalyst. The calculated amount of hydrogen is absorbed within 10 hours. The catalyst is suctioned off, the filtrate is evaporated to dryness under vacuum and the residue crystallized from ethanol, to yield 1 secondary butyl-4-hydroxy-6-para-amino-benzyl-pyrimidine of the formula



in colourless crystals melting at 201—203°C.

EXAMPLE 26

1.65 grams of sodium are added to 50 cc of anhydrous toluene and the mixture is heated with vigorous stirring to 120°C, and at the same temperature a solution of 7 grams of 2 - isopropyl - 3 - amino - 4 - carbethoxy-pyrazole in 19 grams of *p*-chlorobenzyl cyanide is slowly added dropwise. The mixture is heated with stirring during the course of 5 hours to 130°C, allowed to cool, treated with 24 cc of alcohol and evaporated to dryness under vacuum. The residue is taken up in 100 cc of 2N-sodium hydroxide solution, the alkaline solution is agitated with toluene to remove the undissolved material and then adjusted with 6N-hydrochloric acid to a pH value of 5—6, whereupon a solid product precipitates which is recrystallized from a small amount of alcohol, to yield 1 - isopropyl - 4-hydroxy - 6 - (*p* - chlorobenzyl) - pyrazolo-[3,4 - d]pyrimidine of the formula



in colourless crystals melting at 181—182°C.

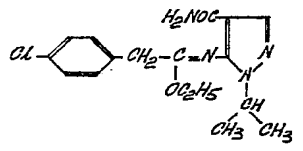
EXAMPLE 27

A mixture of 8 grams of 2-isopropyl-3-amino-4-carbamyl-pyrazole and 26 grams of *p*-chloro-phenylacetic acid amide is heated for 4 hours in a bath maintained at 200—210°C, then allowed to cool and the crystalline residue is pulverised, extracted with 2N-sodium hydroxide solution, treated with active carbon and precipitated by adjusting the reaction mixture with 2N-hydrochloric acid to a pH value of 3. The precipitated product is recrystallized from alcohol, to yield 1 - isopropyl - 4-hydroxy - 6 - (*p* - chloro - benzyl) - pyrazolo-[3,4 - d]pyrimidine in colourless crystals melting at 181—182°C.

EXAMPLE 28

Dry hydrochloric acid is introduced at −10°C into 34.2 grams of para-chlorobenzyl cyanide in 250 cc of chloroform and 13 cc of alcohol until the solution is saturated. The reaction solution is allowed to stand overnight at room temperature and then evaporated at a maximum temperature of 30°C. The residue containing the imino ether hydrochloride is dissolved in 200 cc of chloroform, a suspension of 16.9 grams of 2-isopropyl-3-amino-4-carbonamido-pyrazole in 1800 cc of chloroform is added and the whole boiled under reflux for 10 hours with stirring. Any undissolved material is filtered off and the filtrate evaporated to dryness. The residue

consists of crude 2 - isopropyl - 3 - [α-ethoxy - β - (p - chlorophenyl) - ethylidene-amino] - pyrazole - 4 - carboxylic acid amide of the formula



a) The amide is heated for 10 hours at 180°C. The residue is extracted with 2N-sodium hydroxide solution and chloroform. The aqueous alkaline portion is adjusted to a pH value of 6 with 6N-hydrochloric acid, whereupon the 1 - isopropyl - 4 - hydroxy - 6-para - chlorobenzyl - pyrazolo - [3,4 - d]-pyrimidine described in Example 1 precipitates.

b) 69 grams of the above amide are boiled under reflux for 30 minutes with a solution of 18 grams of sodium in 315 cc of methanol. The reaction solution is filtered and then evaporated and the residue extracted with water and chloroform. The aqueous alkaline solution is neutralized with 6N-hydrochloric acid, whereupon the 1 - isopropyl - 4 - hydroxy - 6 - (para - chlorobenzyl) - pyrazolo-[3,4 - d]pyrimidine described in Example 1 precipitates.

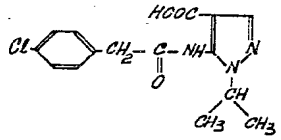
EXAMPLE 29

6.1 grams of 1 - isopropyl - 4 - oxo - 6-(para - chlorobenzyl) - pyrazolo[3,4 - d]-oxazine are heated with 50 cc of benzene and 15 cc of liquid ammonia in a sealed tube for 8 hours at 100—110°C.

2N-sodium hydroxide solution are added to the reaction product and the benzene solution separated. The aqueous alkaline solution is adjusted to a pH value of about 6 with 6N-hydrochloric acid, whereupon 1 - isopropyl-4 - hydroxy - 6 - (para - chlorobenzyl)-pyrazolo[3,4 - d]pyrimidine precipitates.

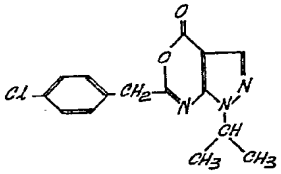
The 1 - isopropyl - 4 - oxo - 6 - para-chlorobenzyl - pyrazolo[3,4 - d]oxazine used as starting material is prepared as follows:

A solution of 92.7 grams of para-chlorophenylacetic acid chloride in 125 cc of dioxane is added dropwise and with stirring to 84.5 grams of 2-isopropyl-3-amino-4-carboxy-pyrazole in 375 cc of absolute dioxane and 40 cc of pyridine at a temperature between 10 and 15°C. When the addition is complete, the mixture is stirred for 1 hour at 10°C and then for 2 hours at room temperature. For the purpose of working up, water and dilute hydrochloric acid are added and the reaction solution is extracted with ether. The ethereal solution is dried and evaporated. The residue is scratched within a glass rod in water and then recrystallized from a mixture of acetone and petroleum ether. 2 - Isopropyl - 3 - (para-chlorophenyl - acetylamino) - 4 - carboxy-pyrazole of the formula



is obtained.

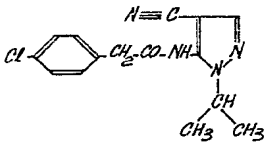
9.7 grams of 2 - isopropyl - 3 - (para-chlorophenylacetylamino) - 4 - carboxy - pyrazole are heated with 30 cc of acetic anhydride for 3 hours at 100—110°C with stirring. The reaction solution is evaporated and the residue recrystallized from a mixture of ether and petroleum ether. 1 - Isopropyl - 4 - oxo - 6-(para - chlorobenzyl) - pyrazolo[3,4 - d]-oxazine of the formula



is obtained.

EXAMPLE 30

A solution of 55.8 grams of para-chlorophenylacetic acid chloride in 75 cc of dioxane is added dropwise to 45.5 grams of 2-isopropyl-3-amino-4-cyano-pyrazole in 325 cc of absolute dioxane and 24 cc of pyridine with stirring at a temperature between 10 and 15°C. When the addition is complete, stirring is continued for 1 hour at 10°C and then for 2 hours at room temperature. After the addition of 100 cc of water and 200 cc of 2N-hydrochloric acid, 2 - isopropyl - 3 - (para-chlorophenylacetylamino) - 4 - pyrazole - carboxylic acid nitrile of the formula



crystallizes out.

7.95 grams of 2 - isopropyl - 3 - (para-chlorophenylacetylamino) - 4 - pyrazole - carboxylic acid nitrile are heated with 27.2 cc of potassium hydroxide solution of 10% strength and 102 cc of hydrogen peroxide of 3% strength for 10 hours at 70°C. The reaction solution is then filtered and acidified with 2N-hydrochloric acid to a pH value of 5, whereupon 1 - isopropyl - 4 - hydroxy - 6-(para - chlorobenzyl) - pyrazole[3,4 - d]-pyrimidine precipitates.

EXAMPLE 31

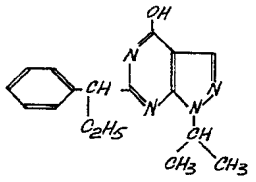
16.5 grams of sodium are finely pulverized in 120 cc of toluene in a sulphurating flask of 750 cc capacity at a bath temperature of 130°C. 240 cc of benzene free from thiophene are then added. 70 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole in 182 grams of para-chlorobenzyl cyanide are added dropwise in the course of 2½ hours at a bath temperature of 120°C and internal temperature of 88—90°C. When the addition is complete, the reaction mixture is boiled under reflux for 10 hours with stirring.

For the purpose of working up, 250 cc of absolute alcohol are added, and the reaction solution is evaporated to dryness. The residue is taken up in 1.2 litres of N-sodium hydroxide solution and extracted three times with 200 cc of toluene. The alkaline solution is adjusted to a pH value of 5—6 with 5N-hydrochloric acid; the crystalline precipitate is filtered off.

The crystalline filter residue is dissolved in 340 cc of alcohol, the solution is treated with carbon and filtered. With ice-cooling, 1-isopropyl - 4 - hydroxy - 6 - para - chlorobenzyl-pyrazolo[3,4 - d]pyrimidine crystallizes out.

EXAMPLE 32

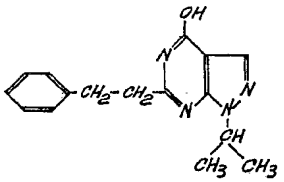
A mixture of 19.7 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole and 49.5 grams of α-phenyl-butyronitrile is added to 4.6 grams of pulverized sodium in 85 cc of absolute toluene at a temperature of 90—95°C with stirring. Stirring is then continued for 5 hours at 90—95°C. For the purpose of working up, 50 cc of alcohol are added and the reaction mixture evaporated to dryness. The residue is extracted with N-sodium hydroxide solution and toluene. The aqueous alkaline solution is adjusted to a pH value of about 6 with 6N-hydrochloric acid, whereupon 1 - isopropyl-4 - hydroxy - 6 - (α - phenyl - propyl)-pyrazolo[3,4 - d] - pyrimidine of the formula



precipitates which, after recrystallization from alcohol, melts at 142—143°C.

EXAMPLE 33

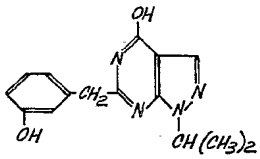
A solution of 19.7 grams of 2-isopropyl-3-amino-4-carbethoxy-pyrazole and 45 grams of β-phenyl-propionitrile in 30 cc of absolute toluene is added to 4.6 grams of pulverised sodium in 85 cc of absolute toluene with stirring at a temperature of 90—95°C. Stirring is then continued for 5 hours at 90—95°C. For the purpose of working up, 50 cc of alcohol are added and the reaction solution is evaporated to dryness. The residue is extracted with N-sodium hydroxide solution and toluene. The aqueous alkaline solution is neutralized with 6N-hydrochloric acid, whereupon 1-isopropyl - 4 - hydroxy - 6 - (β - phenyl - ethyl)-pyrazolo[3,4 - d]pyrimidine of the formula



precipitates which, after recrystallization from alcohol, melts at 124—125°C.

EXAMPLE 34

A solution of 8 grams of 1 - isopropyl - 4-hydroxy - 6 - (*m* - methoxy - benzyl) - pyrazolo[3,4 - d]pyrimidine in 80 cc of 48% hydrobromic acid is heated in an oil bath at 120°C for three hours. The reaction mixture is then poured on ice, its pH value adjusted to 5 with 2N-sodium hydroxide solution, and the precipitate filtered off with suction. On recrystallization from alcohol, 1 - isopropyl-4 - hydroxy - 6 - (*m* - hydroxy - benzyl)-pyrazolo[3,4 - d]pyrimidine of the formula



is obtained in the form of white crystals of melting point 226—227°C.

1 - Isopropyl - 4 - hydroxy - 6 - (*m*-hydroxy - benzyl) - pyrazolo[3,4 - d]pyrimidine can also be obtained by reacting meta-hydroxybenzylcyanide with 2-isopropyl-3-amino-4-carbethoxy-pyrazole according to the method described in Example 1.

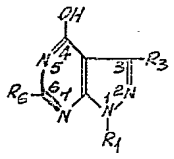
EXAMPLE 35

1 - Isopropyl - 4 - hydroxy - 6 - (para-chlorobenzyl) - pyrazolo[3,4 - d]pyrimidine is made up in the usual manner into tablets containing:

1 - isopropyl - 4 - hydroxy - 6-(*p* - chlorobenzyl) - pyrazolo-[3,4 - d]pyrimidine	10 mg
Lactose	35 mg
Non-swellable starch	20 mg
Wheat starch	10 mg
Silicic acid	10 mg
Arrowroot	12 mg
Magnesium stearate	0.5 mg
Talc	6 mg

WHAT WE CLAIM IS:—

1. A pyrazolo[3,4-d]pyrimidine of the formula

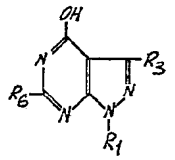


or a tautomer thereof, in which R_1 represents a hydrogen atom or an alkyl, hydroxyalkyl, oxa-alkyl, cycloalkyl, cycloalkylalkyl or aralkyl group or an at most binuclear aryl or heterocyclic group, R_3 represents a hydrogen atom or a lower alkyl group, and R_6 represents an aralkyl group.

2. A salt of a compound as claimed in claim 1.

3. An alkali metal salt of a compound as claimed in claim 1.

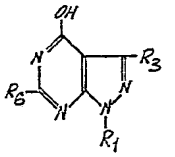
4. A compound of the formula



or a tautomer thereof, in which R_1 represents a hydrogen atom or a lower alkyl, cycloalkyl, hydroxy-lower alkyl, oxa-lower alkyl, aryl or pyridyl group, R_3 represents a hydrogen atom or a lower alkyl group and R_6 represents an aralkyl group.

5. A salt of a compound as claimed in claim 4.

6. A compound of the formula



or a tautomer thereof, in which R_1 represents a lower alkyl group, R_3 represents a hydrogen atom or a lower alkyl group, and R_6 represents an unsubstituted benzyl group or a benzyl group mono-, di- or tri-substituted in the phenyl nucleus by chlorine, methoxy, methylenedioxy, methyl or trifluoromethyl.

7. A salt of a compound as claimed in claim 6.

8. 1 - Isopropyl - 4 - hydroxy - 6 - (para-chlorobenzyl) - pyrazolo - [3,4 - d]pyrimidine.

9. 1 - Isopropyl - 4 - hydroxy - 6 - (meta-methoxybenzyl) - pyrazolo[3,4 - d]pyrimidine.

10. 1 - Isopropyl - 4 - hydroxy - 6-(3^1,4^1,5^1 - trimethoxy - phenylmethyl) - pyrazolo[3,4 - d]pyrimidine.

11. 1 - Pentyl - (3^1) - 4 - hydroxy - 6-benzyl - pyrazolo[3,4 - d]pyrimidine.

12. 1 - Methyl - 4 - hydroxy - 6 - benzyl pyrazolo[3,4 - d]pyrimidine.

13. 1 - Methyl - 4 - hydroxy - 6 - (3^1,4^1,5^1-trimethoxy - phenylmethyl) - pyrazolo - [3,4 - d]pyrimidine.

14. 1 - Isopropyl - 4 - hydroxy - 6 - (para-ethoxybenzyl) - pyrazolo[3,4 - d]pyrimidine.

15. 1 - (Secondary butyl) - 4 - hydroxy - 6-benzyl - pyrazolo[3,4 - d]pyrimidine.

16. 1 - Cyclohexyl - 4 - hydroxy - 6-benzyl - pyrazolo [3,4 - d]pyrimidine.

17. 1 - (Cyclopentyl) - 4 - hydroxy - 6-benzyl - pyrazolo[3,4 - d] - pyrimidine.

18. 1 - (β - Hydroxyethyl) - 4 - hydroxy-6 - benzyl - pyrazolo[3,4 - d]pyrimidine.

19. 1 - [1^1 - Ethoxy - butyl - (3^1)] - 4-hydroxy - 6 - benzyl - pyrazolo[3,4 - d]-pyrimidine.

20. 1 - Methyl - 4 - hydroxy - 6 - (para-chlorobenzyl) - pyrazolo[3,4 - d]pyrimidine.

21. 1 - Methyl - 4 - hydroxy - 6 - (2^1,3^1-dimethoxy - phenyl - methyl) - pyrazolo [3,4-d]pyrimidine.

22. 1 - Phenyl - 4 - hydroxy - 6 - benzyl-pyrazolo[3,4 - d]pyrimidine.

23. 1 - Phenyl - 4 - hydroxy - 6 - (meta-methoxybenzyl) - pyrazolo[3,4 - d]pyrimidine.

24. 1 - (α - Pyridyl) - 4 - hydroxy - 6-benzyl - pyrazolo[3,4 - d]pyrimidine.

25. 4 - Hydroxy - 6 - benzyl - pyrazolo-[3,4 - d]pyrimidine.

26. 1 - Isopropyl - 4 - hydroxy - 6 - (ortho-methoxybenzyl) - pyrazolo[3,4-d]pyrimidine.

27. 1 - Isopropyl - 4 - hydroxy - 6 - (2^1-methyl - 3^1 - methoxyphenyl - methyl) - pyrazolo[3,4 - d]pyrimidine.

28. 1 - Isopropyl - 4 - hydroxy - 6 - di-phenylmethyl - pyrazolo - [3,4 - d]pyrimidine.

29. 1 - [3^1 - Methyl - butyl - (2^1)] - 4-hydroxy - 6 - benzyl - pyrazolo[3,4 - d]-pyrimidine.

30. 1 - (Secondary butyl) - 4 - hydroxy - 6-(para - nitrobenzyl) - pyrazolo[3,4 - d] - pyrimidine.

31. 1 - (Secondary butyl) - 4 - hydroxy-6 - (para - aminobenzyl) - pyrazolo[3,4 - d]-pyrimidine.

32. 1 - Isopropyl - 4 - hydroxy - 6 - (α-phenyl - propyl) - pyrazolo[3,4 - d]pyrimidine.

33. 1 - Isopropyl - 4 - hydroxy - 6 - (β-phenyl - ethyl) - pyrazolo[3,4 - d]pyrimidine.

34. 1 - Isopropyl - 4 - hydroxy - 6 - (meta-hydroxybenzyl) - pyrazolo[3,4 - d]pyrimidine.

35. A salt of the compound claimed in any one of claims 8 to 34.

36. A compound as claimed in claim 1 and described in any one of Examples 1 to 34 herein.

37. A pharmaceutical preparation which comprises a compound as claimed in any one of claims 1, 4 and 6 in admixture or conjunction with a pharmaceutically suitable excipient.

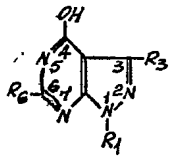
38. A pharmaceutical preparation which comprises a salt as claimed in any one of claims 2, 3, 5 and 7 in admixture or conjunction with a pharmaceutically suitable excipient.

39. A pharmaceutical preparation which comprises the compound claimed in any one of claims 8 to 34 in admixture or conjunction with a pharmaceutically suitable excipient.

40. A pharmaceutical preparation which comprises a salt as claimed in claim 35 in admixture or conjunction with a pharmaceutically suitable excipient.

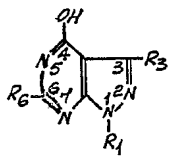
41. A tablet having substantially the composition described in Example 35 herein.

42. A process for the manufacture of a pyrazolo-[3,4-d]pyrimidine of the formula



or a tautomer thereof, or a salt thereof, in which R_1 represents a hydrogen atom or an alkyl, hydroxyalkyl, oxaalkyl, cycloalkyl, cycloalkylalkyl or aralkyl group or an at most binuclear aryl or heterocyclic group, R_3 represents a hydrogen atom or a lower alkyl group, and R_6 represents an aralkyl group, wherein a 2 - R_1 - 3 - amino - 5 - R_3 - pyrazole - 4-carboxylic acid ester is reacted with a carboxylic acid of the formula R_6-COOH in the form of its amide or nitrile, or a 2-R_1-3-amino-5-R_3-pyrazole-4-carboxylic acid amide is reacted with a carboxylic acid of the formula R_6-COOH in the form of its anhydride, or amide, or with a corresponding halide or nitrile.

43. A process for the manufacture of a pyrazolo[3,4-d]pyrimidine of the formula



or a tautomer thereof, or a salt thereof, in which R_1 represents a hydrogen atom or an alkyl, hydroxyalkyl, oxaalkyl, cycloalkyl, cycloalkylalkyl or aralkyl group or an at most binuclear aryl or heterocyclic group, R_3 represents a hydrogen atom or a lower alkyl group, and R_6 represents an aralkyl group, wherein a 2 - R_1 - 3 - amino - 5 - R_3 - pyrazole - 4-carboxylic acid ester is reacted with a nitrile of the formula R_6-CN.

44. A process for the manufacture of a pyrazolo-pyrimidine conducted substantially as described in any one of Examples 1 to 34 herein.

45. A compound as claimed in claim 1 and obtained by the process claimed in claim 43 or 44.

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